Bioequivalence Approaches for Long-Acting Drug Products: Regulatory and Scientific Considerations

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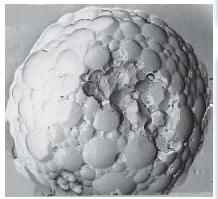
Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Long-Acting Drugs

- Systemic acting
  - Oil-based injectable solutions
  - Injectable-drug suspensions
  - Polymer based implants and in-situ forming implants
  - Polymer based microparticles

- Local acting
  - Polymer based microparticles
  - Lipid based microparticles (multivesicular liposomes)
  - Intrauterine devices/systems
  - Intravaginal rings



Complex drug products

Challenges in Generic Development of Long Acting Drugs

- Complex formulation and excipients
- Small process and raw material changes could result in significant product changes
- Complicated characterizations
- No standard in vitro drug release assay
- Release mechanisms (especially in vivo) are not fully understood
- Few models correlating in vitro drug release with in vivo pharmacokinetics
- Complicated bioequivalence study design (i.e. prolong study duration, study population)
- …….

General Regulatory and Scientific Considerations on Bioequivalence Approach

Regulatory considerations:

- Route of administration: Qualitative (Q1) and quantitative(Q2) sameness of excipients
- Pharmaceutical equivalence: complex active ingredient sameness

Scientific considerations:

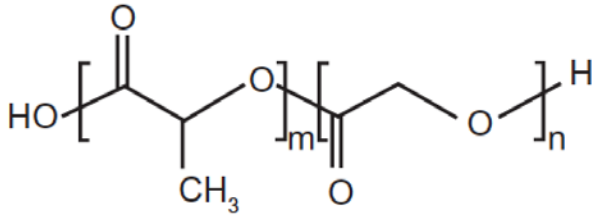
- Healthy volunteers ***vs*** patients
- Single dose ***vs*** steady state
- Pharmacokinetic endpoints ***vs*** clinical endpoints
- In vivo studies ***vs*** in vivo studies in combination with in vitro studies ***vs*** in vitro only approaches
- ……

Polymer Based Microparticles

Regulatory considerations:

Q1/Q2 sameness of excipients (☹)

- **Poly(lactic-*co*-glycolic acid) (PLGA) copolymer**

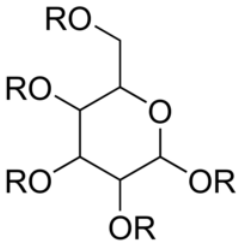


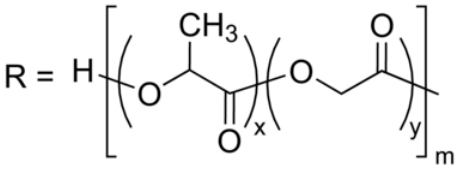
PLGA

m = number of units of lactic acid
n = number of units of glycolic acid

- Ratio of lactic acid to glycolic acid
- Molecular weight ~5kDa -100kDa

- **Glucose star polymer, D,L-lactic and glycolic acids copolymer**





Sandostatin LAR depot
(octreotide acetate microsphere)

Polymer Based Microparticles (Cont.)

Regulatory actions: GDUFA Research Programs

Frequently cited by firms in Q1/Q2 controls

International Journal of Pharmaceutics 495 (2015) 87–92
Contents lists available at ScienceDirect
International Journal of Pharmaceutics
journal homepage: www.elsevier.com/locate/ijpharm

A protocol for assay of poly(lactide-*co*-glycolide) in clinical products

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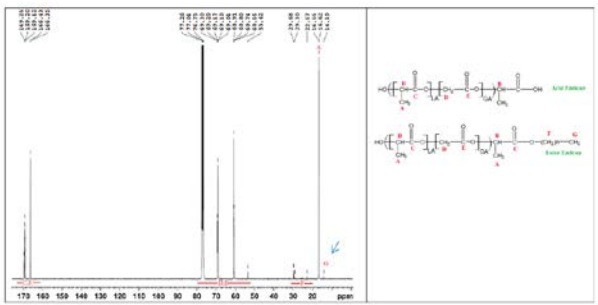

Table 1
M_n,M_w, and PDI as determined by GPC.

Sample	M_n	M_W	PDI
Trelstar®	25,192 Da	85,207 Da	3.38
Risperdal Consta®	44,875 Da	111,142 Da	2.48
AP024*	43,519 Da	74,870 Da	1.72
AP122*	75,704 Da	116,479 Da	1.54

* Neat polymer prior to formulation into microparticles.

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journal homepage: www.elsevier.com/locate/jconrel

Complex sameness: Separation of mixed poly(lactide-*co*-glycolide)s based on the lactide:glycolide ratio

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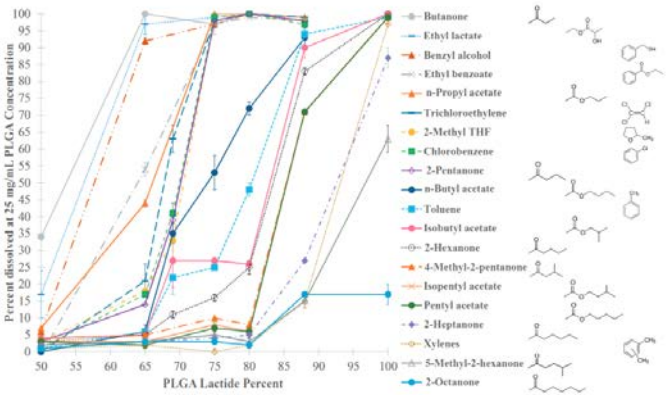

Fig. 2. Dissolution of PLGAs in solvents as a function of the lactide content (or L:G ratio) at 30 °C. The 100% dissolution indicates complete dissolution at the concentration of 25 mg/mL.

Separation of PLGA mixtures when used in the same product is possible!

https://www.google.com/search?biw=1536&bih=775&tbm=isch&sa=1&ei=NDIyXZ2DLdDL_QbFr7ulDg&q=rescue+research&oq=rescue+research&gs_l=img.3...175.6.2990..3.315...0.0..0.73.604.9.....0....1..gws-wiz-img.....0i67j0j0i5i30j0i8i30j0i24.WkWAiwpBISw&ved=0ahUKEwid7dT08sHjAhXQct8KHcXXDuEQ4dUDCAY&uact=5#imgrc=_7INjkQXRluwdLM:

Polymer Based Microparticles (Cont.)

Regulatory actions: GDUFA Research Programs

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Characterization of branched poly(lactide-*co*-glycolide) polymers used in injectable, long-acting formulations

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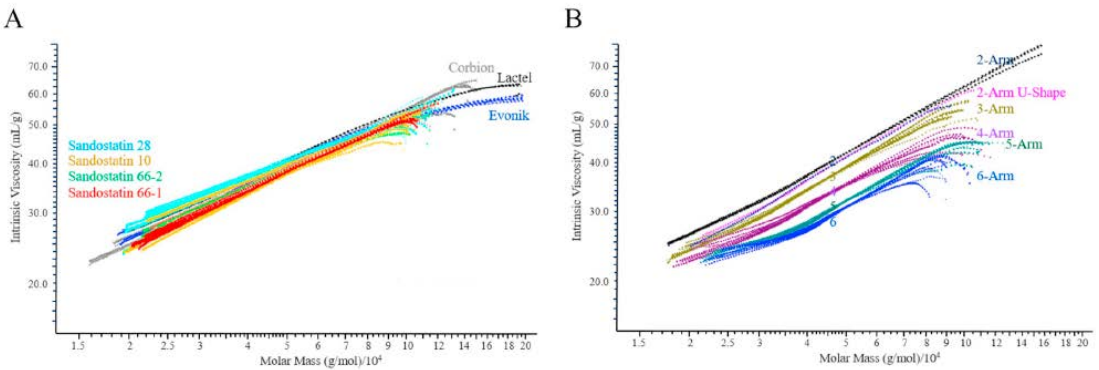
Ensemble characterization of Glu-PLGA using 10 parameters.

Parameter	Method	Property
1) L:G ratio	^{1}H-NMR	This affects PLGA properties, in particular, solubility in solvents.
2) Glycolide blockiness (R_c)	$\frac{I_{G-G}}{I_{G-L}}$	This affects solvent solubility.
3) Absolute weight average molecular weight (M_w)	Static light scattering detector with GPC	This is important for the Mark-Houwink plot.
4) Absolute number average molecular weight (M_n)	Osmometer	This value can be replaced with the number average molecular weight (M_n) from GPC.[a]
5) Polydispersity index of Glu-PLGA (PDI_b)	$\frac{M_{w,b}}{M_{n,b}}$	This indicates the broadness of a molecular weight distribution.
6) Molecular weight distribution	GPC with static light scattering detector	This allows calculation of percent fractions of different molecular weights.
7) Intrinsic viscosity ([η])	Online viscometer with GPC	This is essential for the Mark-Houwink plot.
8) Drainage factor (e)	$g' = g^e$	The lower e, the higher branch units.
9) Number of branches (or arms) (B)	$g = \left(\frac{< R_g^2 >}{< R_g^2 >}\right)_M$	This describes the branch units from a glucose core.
10) Polydispersity index of arms ($PDI_{b,arm}$)	$B\left(\frac{M_{w,b}}{M_{n,b}} - 1\right) + 1$	This indicates the heterogeneity of PLGA arms on a glucose core.

[a] Osmometer requires a large amount of a sample which may not be available for clinical formulations.



The first research report on characterization of glucose-PLGA star polymer. The developed method is not reference standard dependent.

Evaluated glucose-PLGA polymers from all suppliers in the U.S. and compared them to the polymer extracted from the brand product.

Long Acting Injectable Suspensions

Regulatory considerations:

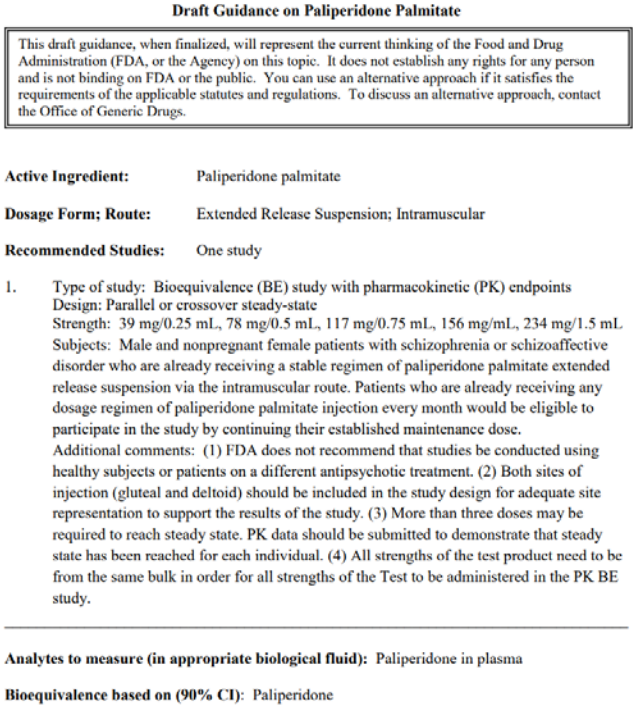
Q1/Q2 sameness of excipients (☺)

Scientific considerations:

Healthy volunteers vs patients: Antipsychotic drugs - Safety - Patients

Single dose vs steady state: Patients – Ethics – Steady state (no switch between different drugs)

- ➢Long study duration
- ➢Potential high drop-out rate
- ➢Large number of subjects



Draft Guidance on Paliperidone Palmitate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Paliperidone palmitate

Dosage Form; Route: Extended Release Suspension; Intramuscular

Recommended Studies: One study

1. Type of study: Bioequivalence (BE) study with pharmacokinetic (PK) endpoints
   Design: Parallel or crossover steady-state
   Strength: 39 mg/0.25 mL, 78 mg/0.5 mL, 117 mg/0.75 mL, 156 mg/mL, 234 mg/1.5 mL
   Subjects: Male and nonpregnant female patients with schizophrenia or schizoaffective disorder who are already receiving a stable regimen of paliperidone palmitate extended release suspension via the intramuscular route. Patients who are already receiving any dosage regimen of paliperidone palmitate injection every month would be eligible to participate in the study by continuing their established maintenance dose.
   Additional comments: (1) FDA does not recommend that studies be conducted using healthy subjects or patients on a different antipsychotic treatment. (2) Both sites of injection (gluteal and deltoid) should be included in the study design for adequate site representation to support the results of the study. (3) More than three doses may be required to reach steady state. PK data should be submitted to demonstrate that steady state has been reached for each individual. (4) All strengths of the test product need to be from the same bulk in order for all strengths of the Test to be administered in the PK BE study.

Analytes to measure (in appropriate biological fluid): Paliperidone in plasma

Bioequivalence based on (90% CI): Paliperidone

Long Acting Injectable Suspensions (Cont.)

In vivo studies ***vs*** in vitro based totality of evidence approach

Long acting suspensions ***vs*** other injectable suspensions

The prolonged in vivo application duration and the antipsychotic indication of the long acting suspensions present a higher risk compared to injectable suspensions for short term use (i.e., Kenalog 40)

- What are critical quality attributes of long acting suspensions?
- How physiochemical characteristics correlate with in vitro/in vivo drug release?
- How in vitro drug release testing correlates with in vivo bioavailability?

Multivesicular Liposomes

Draft Guidance on Bupivacaine

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Active Ingredient: Bupivacaine

Dosage Form; Route: Injectable, liposomal; injection

Recommended Studies: One study

When the test and reference multivesicular liposome products:

- Have the same drug product composition and
- Have equivalent liposome characteristics including liposome composition, amount of free and encapsulated drug, internal environment of liposome, liposomal particle structure and morphology, liposome size distribution, electrical surface potential or charge, and in vitro release rates.

The following clinical study is recommended to demonstrate bioequivalence:

Pharmacokinetic (PK) bioequivalence study:

Type of study: Fasting*

Design: Single-dose, two-way crossover in-vivo

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Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Probing the mechanism of bupivacaine drug release from multivesicular liposomes

Soumyarwit Manna[a,b], Yong Wu[b], Yan Wang[a], Bonhye Koo[a,b], Lynn Chen[a,b], Peter Petrochenko[a], Yixuan Dong[c], Stephanie Choi[a], Darby Kozak[a], Berk Oktem[b], Xiaoming Xu[c,*], Jiwen Zheng[b,*]

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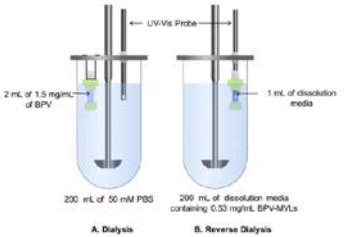

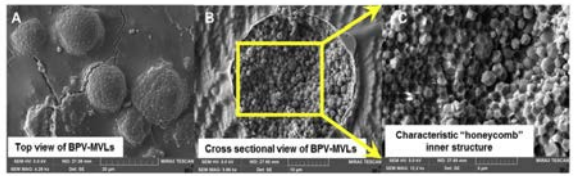

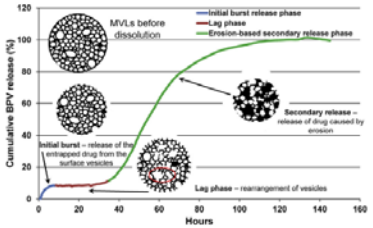

Fig. 11. Schematic detailing possible release mechanism of BPV from the MVLs.

- The potential release mechanisms of MVL was investigated for the first time using advance imaging techniques and a novel in vitro release testing method.

Intrauterine Systems

Our current thinking:

1. A Test IUS should be qualitatively (Q1) and quantitatively (Q2) similar to the RLD and has equivalent physical dimension.
2. Comparative physicochemical and mechanical characteristics between the Test and the RLD.
3. Comparative in vitro drug release profile throughout the intended period of product use (i.e., 5 Y).
4. Comparative short term in vivo study:
   - Ex vivo evaluation (following device insertion and removal): residual LNG
   - Serum drug concentrations (supporting evident)


International Journal of Pharmaceutics 550 (2018) 447–454

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Manufacturing and characterization of long-acting levonorgestrel intrauterine systems

Quanying Bao[a], Bing Gu[a], Claire F. Price[a], Yuan Zou[b], Yan Wang[b], Darby Kozak[b], Stephanie Choi[b], Diane J. Burgess[b,*]

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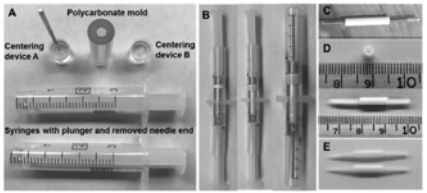
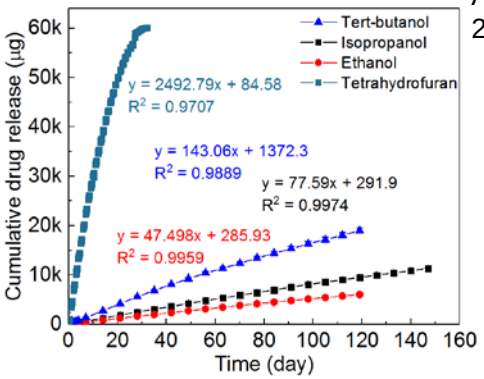
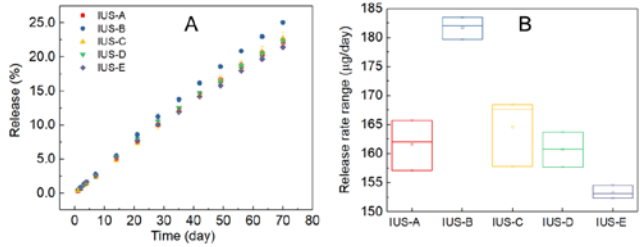




Accelerated drug release using organic solvents
2018 AAPS meeting abstract

Solvents	Release rate (mcg/d)	Swelling ratio
EtOH	47.50	1
IPA	77.59	1.63
TBA	143.06	3.01
THF	2492.79	52.48



Release profiles of IUSs prepared using outer membranes from different sources under accelerated conditions

2019 AAPS meeting abstract

Summary

- Development of product-specific guidances involves significant amount of regulatory and scientific considerations.
- GDUFA research projects have been very helpful for addressing remaining scientific gaps. Pay attention to meeting abstracts, posters, and publications on outcomes of GDUFA research projects.
- OGD is open to novel alternative approaches for assessing bioequivalence of complex long-acting drugs. Engage with us early and provide sufficient information/data to support your proposal in either controlled correspondences or pre-ANDA meeting requests.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